Introduction

During the last decades, the relatively high incidence of head and neck carcinoma has been reported. Head and neck cancers (HNC) represent the sixth most common cancer worldwide with approximately 550,000 new patients diagnosed every year resulting in more than 300,000 deaths annually[1].

There has been a substantial improvement in the treatment of head and neck cancer [2]. Radiotherapy is currently a widely used and important part of this treatment. It can be used as a sole treatment or associated with surgery and/or chemotherapy[3].

Compared with surgical procedures, it shows better results because it can be used as a curative, adjuvant, and palliative type of treatment, and is often used in conservative approaches[4]. It semi selectively destroys cancer cells while preserving normal cells[5].

Head and neck radiotherapy usually consists of cumulative doses that are fractionated and delivered in daily sessions with pauses on weekends. The treatment usually lasts for about 7 weeks and its total doses range from 40 to 70 Gy depending on several factors as tissue response [6, 7].

However, Ionizing radiation has numerous adverse reactions or complications which are more evident in the head and neck region where a variety of highly radiosensitive

structures are found [8]. These complications may be mucositis, xerostomia, osteoradionecrosis, and radiation caries…etc.[9-11].

This highlights the need for special dental care for cancer patients subjected to head and neck radiotherapy. These patients commonly have dental restorations fabricated of a variety of dental materials [12]. Also, physicians often recommend dental treatment to patients just before head and neck radiotherapy.

Such treatment usually requires replacement of metal-based restorations by polymer-based restorative materials (ionizing radiation interacts with metallic materials such as amalgam, intensifying the radiation in the surroundings of the material. This secondary irradiation depends mainly on the atomic number of the material's components. Therefore, this effect should be reduced in polymer-based materials since they absorb radiation) [13].

The need for high performance and stability of the restorative materials used in these cases is a must.

Resin-based dental restorations such as dental composites, resin modified glass ionomers, and compomers are tooth-colored restorative material with extensive applications in dentistry. They are widely used as restorative materials because of their good clinical performance [14].

Till now, most reported studies about clinical failures of these restorations after radiotherapy may be associated to interfacial bonding, with very little information on the restorative materials itself.

In this context, the assessment of some mechanical and physical properties of three different dental esthetic restorative materials; before and after exposure to the therapeutic dose of radiotherapy; could show the effect of radiotherapy on these materials, and consequently allow the clinicians to choose the best material in these situations.

Review of Literature

1. Head and neck cancer:

1.1. Incidence:

Head and neck cancer (HNC) is a major international public health issue[15]. It summarizes a variety of cancer sites and histological types [16].

The worldwide annual incidence of HNC is over 550,000 cases, with about 300,000 deaths each year[1]. The male to female ratio ranges between 2:1 and 4:1, and in many parts of the world, the prevalence is increasing [17].

About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC), which is considered one of the most common cancers worldwide [18]. It is the sixth driving cancer by occurrence around the world.

Most of the HNSCCs arise in the oral cavity, oropharynx, larynx, and hypo-pharynx epithelial lining. HNSCC is a heterogeneous disease that is strongly related to certain environmental and lifestyle risk factors such as tobacco and alcohol use. Recently, a new disease has emerged related to several strains of human papilloma virus (HPV 16,18)[19].

Nowadays, it is well known that not only smokers and drinkers who may develop HNSCC, although they still have a great influence. There are many other risk factors involved in

the appearance of HNSCC. Carcinogen exposure, chronic irritation to the lining mucosa of the mouth, oral hygiene, dental plaque formation, family history, low body mass index, and exposure to ultraviolet light also play an important role in the HNSCC development as they can modulate the toxin and carcinogenic metabolism [20, 21].

Importantly, the 5-year survival rate of HNSCC patients is only 40–50% (19). HNSCC has been known to have a high incidence of lymph node metastasis, with over two-thirds of patients presenting with regional lymph node involvement, and 10% presenting with distant metastases[22].

The high mortality rate is attributed to a high rate of late diagnosis, and the survival rate for cases in late stages is only 34.9% [23].

1.2. Head and Neck Cancer Treatment Modalities:

HNSCC is the most complex “organ site”, as the region's anatomy is topographically complex and densely populated by vital structures, nerves, and vascular and lymphatic structures [24], so the treatment decision is not an easy decision.

It is beyond our scope in this thesis to give a full detailed review of different types of cancer therapy. Brief comments on cancer treatment modalities, will be made to give a general picture of contemporary mainstream cancer therapies.

Generally, treatment of any cancer aims to remove or destroy the cancerous cells without killing normal cells [25]. The most common treatment modalities of HNSCC include surgery, radiotherapy and chemotherapy either alone or in different combinations [26].

The use of surgery, radiation, and/or chemotherapy depends on many factors such as age of the patient, tumor type, size, location, and stage of the cancer, as well as whether an organ preservation approach is feasible.

Surgical therapy is the main treatment option for primary and secondary malignancy as well as recurrent disease [27]. It is often followed by the treatment of radiotherapy or chemotherapy.

Although the primary goal of head and neck surgery is to obtain negative surgical margins, achieving this may be impossible in some cases because of infiltration of vital structures such as the carotid artery or the prevertebral fasciae. It may also cause impairment in important functions such as chewing, swallowing, and speech, and adversely affect the quality of life as it may be disfiguring and psychologically traumatic[28].

The positive surgical margin status is usually associated with decreased survival; therefore, if the tumor has not been completely removed a patient should be re-operated.

Chemotherapy is a therapeutic modality that uses a single drug or a combination of drugs that can impair mitosis, or prevent cell division, trigger apoptosis of cancer cells or stop the growth of new tumor-supplying blood vessels.

Chemotherapeutic drugs can either be delivered directly into the bloodstream, or they can be targeted to a specific cancer site.

However, the nature of chemotherapy means that while damaging cancer cells it will also damages healthy cells, leading to side effects such as hair loss, anemia, nausea, vomiting, diarrhea, and oral infections [(29)].

Radiotherapy is one of the most important treatment modality for head and neck cancer[(30)]. It uses high-energy rays to destroy the head and neck cancer cells, while causing as little damage as possible to healthy tissue.

Generally, single-modality treatment may be chosen for early-stage disease while a combination of two or more treatment modalities is an alternative for patients with advanced head and neck carcinomas to increase tumor control and preserve organ integrity[(31)].

2. Radiotherapy:

2.1. What is radiotherapy:

Radiotherapy, also referred to as radiation therapy (RT), is a treatment method based on the use of high energy rays known as ionizing radiation to damage tumor cells and to limit their growth and division[32].

Radiotherapy has been a very effective tool for treating different kinds of cancer for more than 100 years. It is estimated that about two-thirds of cancer patients will receive RT as a unique treatment or as a part of the more complex therapeutic protocol.

RT can be used alone or often given in association with other treatments. It may be used after surgery with or without chemotherapy, or in combination with chemotherapy, without surgery[33]. Generally, the choice of the proper treatment to be used depends on many factors such as the localization, size, and type of cancer.

2.2. Types of radiations useful in radiotherapy:

Radiotherapy is based on the use of high energy radiation called "ionizing radiation" which is defined as any radiation consisting of electromagnetic waves or moving particles that have sufficient energy to produce ions in matter and tissues[34].

Ionizing radiations may be of two main types: electromagnetic or corpuscular radiation.

Electromagnetic radiations consist of a stream of high photons and have no mass or charge. They include X-rays and gamma-rays.

Corpuscular radiations consist of particles that have an electric charge and mass. They include α and β particles, electrons, protons and neutrons[35].

X-rays and gamma rays are routinely used. X-rays are generated by apparatus that excite electrons (e.g. cathode ray tubes and linear accelerators), while gamma rays originate from the decay of radioactive substances (e.g.cobalt-60, radium, and cesium)[36].

2.3. Mechanism of radiotherapy:

The main goal of RT is to deprive cancer cells of their multiplication potential and eventually kill the cancer cells by a variety of mechanisms.

Radiations may be delivered externally where the source of radiation is external to the body, or internally in which a radioactive source is placed inside the lesions.

Ionizing radiation can easily penetrate the body tissues and deposits its high energy to tissue cells producing free radicals, which damages the genetic material (DNA) of cancer

cells[37]. This can kill cancer cells or cause genetic changes resulting in cancer cell death [38].

2.4. Recent advances in radiotherapy:

Technical advances in radiotherapy are continuously emerging.

Intensity-modulated radiotherapy (IMRT): it is one of the most recent developments in radiotherapy. It has been considered as a very important radiotherapy technique in the management of H & N cancers[39].

It is a computer-controlled technique by which the intensity of radiation can be modulated to create irregular-shaped radiation doses that conform to the complex shaped tumor whilst simultaneously avoiding critical organs, so that a higher precise radiation dose can be delivered to the targets with a sharply conformal target volume coverage, while at the same time the dose to the surrounding normal tissues is markedly reduced[40]. For example, parotid preservation could be performed using IMRT to prevent patients from experiencing severe xerostomia after radiotherapy[41].

IMRT is now available in many clinical departments and can be delivered by linear accelerators machines.

Although modern treatments advocate the use of linear accelerators, appropriately fitted gamma radiation units are still

fully accepted in the treatment of a large majority of the patients undergoing radiotherapy for the head-neck region.

2.5. Gamma radiation:

Gamma radiation is a form of the high-energy ionizing electromagnetic radiation given off by an atomic nucleus undergoing radioactive decay. Gamma rays have the highest frequency and energy (above 100 keV), and also the shortest wavelength in the electromagnetic spectrum [(42)].

The radioactive isotopes, cobalt-60, and cesium-137 are considered the main sources of gamma radiation due to their high energetic value of radiation and reliability.

Because of their high energy, gamma photons travel at the speed of light with a very high penetrating power. They can pass through many types of materials, including human tissue. As it passes through matter, gamma radiation ionizes matter atoms and creates charged particles and free radicals [(43)].

Gamma rays are used in many fields such as medicine (radiotherapy), industry (sterilization and disinfection) and the nuclear industry[(44)].

Many hypotheses attempted to explain the mechanism of cell injury caused by gamma rays [(45)]. It is now widely accepted that damage of (DNA) is mainly responsible for the detrimental effects of gamma radiation [(46)]

Gamma rays either destruct the DNA helix directly or indirectly by generating free radicals that will cause damage to the cell components and breaks in the DNA structure. The cell can no longer reproduce and the result is cell death [47]

2.6. Radiation dose:

The specific radiation dose for each patient is determined by the oncologist responsible for therapeutic decisions. It depends on the location, size, and severity of the tumor and many other factors.

Radiation doses are expressed in a standard unit called "gray (Gy)", which is a measure of the amount of radiation energy absorbed by 1 kilogram of human tissue [48].

2.7. Dose Fractioning:

It means that the total radiation dose is usually divided into several fractions. Each fraction contains a small amount of radiation which accumulates gradually to form the total dose. So the patient is subjected to smaller but more frequent doses of radiation.

Typically, for the most of HNC patients, a dose of 2 Gy per fraction is delivered once a day, five days per week, over a five-to-seven-week period with a total dosage of (50-70 Gy)[49] [50].

This technique maximizes the radiation dose to abnormal cancer cells while minimizing damage of normal cells adjacent to cancer cells or in the path of radiation.

This may be due to the fact that normal cells proliferate relatively more slowly compared to the rapidly proliferating cancer cells and therefore have time to repair the damage before replication [38]. Also, cancer cells are not efficient as normal cells in repairing the damage caused by radiation treatment resulting in differential killing of cancer cell [51].

2.8. Advantages of radiotherapy:

In chemotherapy, the used chemical drugs are not so "specific" and they get into the bloodstream exposing the whole body to cancer-fighting drugs, so they affect normal cells with a high turnover rate such as bone marrow cells, hair follicle cells, and the epithelial cells of the gastrointestinal tract. This may be associated with hematologic toxicities (anemia, leukopenia, and thrombocytopenia), fatigue, nausea and vomiting, hair loss, loss of appetite, and diarrhea [52].

Surgical treatment of HNC may be associated with long-term complications ranging from aesthetic considerations such as severe facial disfigurement, to impaired function (speech, mastication or swallowing, breathing) thus resulting in emotional and psychological distress impairing their quality of life [53, 54].

Unlike chemotherapy and surgery, radiotherapy is usually considered as a local treatment that is aimed at only the part of the body being treated thus damaging cancer cells, with as little damage to healthy cells nearby as possible.

Also, radiotherapy allows the preservation of many vital functions, such as natural speech and swallowing [55].

Recently, advances in RT helped to limit their side effects by fractioning the total dose of irradiation so that normal tissue can recover and repair itself to achieve higher survival rates [56] or by precisely focusing the radiation beam on the tumor to decrease radiation exposure of normal tissues by use of intensity-modulated radiation therapy (IMRT)[39].

2.9. Side effects of radiotherapy:

Although the main aim of radiotherapy is to deliver a concentrated and lethal dose of radiation to the tumor cells to promote healing, penetration of the normal tissues located in the radiation field by ionizing radiation may also damage normal cells by the same mechanism, thus producing a series of toxicities to non-targeted healthy tissues surrounding the tumor[57, 58] These adverse effects depend on the dose amount and rate of radiation [59]

A significant number of HNC irradiated patients experienced several undesired radiation adverse effects during or after the completion of therapy such as mucositis,

xerostomia, loss of taste, dental caries, infection, trismus, and osteoradionecrosis [60, 61].

Unfortunately, these adverse effects can affect patient's everyday functions such as talking, chewing, tasting, and swallowing and significantly decrease his quality of life [62, 63]

The oral complications of head and neck radiation can be classified as acute or late. Acute complications develop during or shortly after the completion of treatment and are usually temporary. It includes oropharyngeal mucositis, sialadenitis, xerostomia, infections (primarily candidiasis), and taste dysfunction [64].

Chronic (late) complications present months to years after the completion of treatment and might be more problematic because they may be lifelong in cancer survivors (52). It may include xerostomia, Trismus and fibrosis, radiation caries, osteoradionecrosis, taste dysfunction, and dysphagia [65].

- **Trismus:**

According to the literature, about 5% to 38% of the patients develop trismus after receiving radiation therapy for head and neck cancer[66]. It is a prolonged spasm of the jaw muscles by which the normal opening of the mouth is restricted[67]. This marked restriction of jaw movements may be due to fibrosis of masticatory muscles or TMJ disorder.